IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Markku Antilla	Examiner: Shirley V. Gembeh
Serial No: 10/777,211	Group Art Unit: 1614
Filed: February 13, 2004	Conf. No.: 2487
For: Method For Enhancing the Bioavailability of Ospemifene	

DECLARATION OF RISTO LAMMINTAUSTA

I, Risto Lammintausta, do hereby make the following declarations:

1. I am Managing Director, Hormos Medical Oy, Turku, Finland and a member of the management board of the parent company, QuatRx Pharmaceuticals Company. I have been employed at Hormos since 1997.

2. I reside at Meltoistentie 29, 20900 Turku, Finland

3. I received a M.D. from the University of Turku, Turku, Finland in 1974. I received a Ph.D. in Clinical Pharmacology from the University of Turku, Turku, Finland in 1978.

4. My credentials are set forth in my curriculum vitae (Exhibit A), that is submitted concurrently herewith.

5. I have read the contents of the Office Action in U.S. Patent Application No. 10/777,211 and in particular the Examiner's rejection of claims 1, 3-5 and 7-20 as being obvious over Anttila M.; Effect of food on the pharmacokinetics of toremifene; Eur. J. Cancer, 33, suppl. 8:1144 (1997) ("Anttila") in view of U.S. Pat. No. 5,750,576 ("DeGregorio et al.") and U.S. Pat. No. 6,387,920 ("Huebner et al.") as evidenced by Kangas L. Biochemical and

pharmacological effects of toremifene metabolites; Cancer Chemother. Pharmacol. 27:8-12 (1990) ("Kangas").

6. Ospemifene is a selective estrogen receptor modulator or a "SERM." A SERM, by definition, displays estrogenicity in at least some tissues (i.e., agonism), but may have no estrogen effect in other tissues, and may in fact block estrogen action in some tissues (i.e. antagonism). (Burger HG: Selective Estrogen Receptor Modulators. Horm.Res.2000;53 Suppl 3:25-29)

7. Prior to the present invention it was known that estrogen has a variety of physiological effects in a large number of tissues in the human body.

8. In contrast, current evidence suggests that each SERM shows some differences from estrogen, as well as from every other SERM.

9. Ospemifene, for example, has the ability to act as an estrogen in some tissues (such as the vagina) and as an antiestrogen in other tissues (such as the breast).

10. Current evidence suggests that the pharmacology of SERMs with respect to their estrogen-mediated effects is potentially unique to each member of the class.

11. Each SERM has the potential to induce an absolutely unique set of pharmacological effects.

12. There is no generalized theory for SERMs such that upon seeing a dose dependent response as to a positive effect, one would not know whether a comparable dose dependent response as to negative effects would occur.

13. Human clinical trials are required to establish most human effects of SERMs.

14. Animal studies involving the administration of SERMs may provide hints to eventual human effects, but these are not necessarily definitive.

15. That is to say, it is difficult to predict the full spectrum of effects in humans based on animal studies involving the administration of SERMs.

16. For example, by late 1993 it had become apparent that tamoxifen (another SERM) had positive effects in the breast, but had serious adverse estrogenic effect in the uterus.Seoud MA et al: Gynecological tumors in tamoxifen treated women with breast cancer. Obtet.Gynecol;1993;82:165-9 Specifically, increased risk of endometrial cancer associated with tamoxifen administration has limited its long-term use.

17. The adverse effects of SERM administration may be determinable only after long-term administration. The effects of tamoxifen on endometrial cancer, for example, were only fully realized after analyses of large, long-term (greater than 5 years) trials.

18. At the time of the invention, it was not publicly known what effect food intake had on the bioavailability of ospemifene in humans.

19. Contrary to the Examiner's assertions, Anttila does not disclose administering a metabolite of toremifene. Anttila discloses administering 60 mg tablets of toremifene. Anttila does measure the blood levels of a major metabolite of toremifene, namely N-demethyltoremifene (or desmethyltoremifene), but no metabolite was administered.

20. The Examiner's conclusion, that administration of a drug that metabolizes to the active form in vivo is the same as administering the metabolite, is true only in the case of compound, which itself is inactive, but through metabolism becomes active. Such compounds are called prodrugs. This is not the case with e.g. toremifene, where the parent drug is the most active compound and thus dominates the clinical tissue specific profile of toremifene.

21. In this case, ospemifene is a minor metabolite of toremifene which does not contribute to the effect of toremifene and its main metabolite desmethyltoremifene as breast cancer treatment compounds. Ospemifene in therapeutic doses demonstrates a therapeutic profile to treat vaginal atrophy, an estrogen agonizing effect, which is an opposite effect versus that of toremifene antagonizing the estrogen effect also in the vaginal epithelium.

22. Although ospemifene and toremifene are structural relatives, their pharmacokinetics are significantly different: when toremifene has elimination half-life of one week, ospemifene is metabolized much faster, with elimination half-life of one day. The metabolites of ospemifene, 4-OH and 4'-OH ospemifene are active compounds contributing to the effect of ospemifene in vaginal atrophy, but these metabolites are either not formed from toremifene at all or they are present only in quantities below the detection limits. (Anttila M et al : Pharmacokinetics of toremifene.J Steroid Biochem 1990;36:249-52)

23. The Examiner is also incorrect in his assertion that food would inherently enhance the bioavailability of toremifene. The Anttila reference teaches that toremifene "works equally well with or without administration of

food." Given the findings in Anttila and the known unpredictability of SERMs in general, one could not have predicted that co-administering ospemifene with food in an amount that causes secretion of bile acids would enhance the bioavailability of ospemifene.

24. The DeGregorio et al. reference relates to the use of ospemifene to treat or prevent osteoporosis. The DeGregorio et al. reference does not teach the administration of a drug with a meal nor does it teach the use of ospemifene to treat either vaginal atrophy or symptoms thereof.

25. Huebner et al. relate to structurally unrelated isoxazole estrogen receptor agonist and antagonist compounds. The isoxazole compounds are said to have utility in preventing or treating estrogen receptor-mediated disorders such as osteoporosis, breast and endometrial cancers. The biological results provided by Huebner et al. confirm the unpredictability of the isoxazoles in that some of the isoxazoles are estrogen agonists and some are estrogen antagonists in various assays and animal models described therein. Moreover, Huebner et al. is silent regarding orally administering any compound, much less ospemifene, to an individual in connection with the intake of a food to enhance bioavailability of the compound.

26. Kangas establishes that ospemifene is a minor metabolite of toremifene. Kangas is silent regarding orally administering any compound, much less ospemifene, to an individual in connection with the intake of a food to enhance bioavailability of the compound.

27. Therefore, in my opinion the teachings of Anttila, DeGregorio et al., Huebner et al., and Kangas, either alone or in combination, do not suggest that the bioavailability of orally administered ospemifene would be enhanced by co-administering the ospemifene with food.

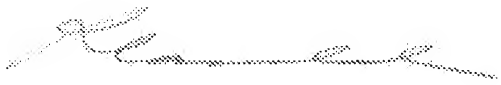
28. On the other hand the unexpected finding of significant 2-3 fold improvement of ospemifene bioavailability with food has very significant practical consequences. It is known from a large clinical study, that ospemifene at 60 mg daily doses given with food shows significant benefit in dyspareunia, a symptom of vaginal atrophy. Since the regulators are insisting the use of the lowest effective dose of drugs for these kind of non-fatal disorders, it is critically important that the patient is advised to take the drug with food. This is not the case with other SERM class compounds in clinical use. Especially for toremifene, the closest chemical relative of ospemifene in the clinical use, the tablets can be taken with or without food, according to Anttila.

29. In further studies after this invention it has been demonstrated in vitro, that the bile acids secreted after food and not the food itself is the critical factor in increasing the absorption on ospemifene. If we compare the dissolution of ospemifene tablets in simulated intestinal fluid representing the fasted state to the fluid representing the fed state, we see 3 times higher dissolution in the fed state. The main difference between those fluids in vitro being the increased amount of taurocholate, the principal bile acid secreted after a meal. Therefore, instead of specifying the contents of food, the attribute of food to be able to stimulate biliary secretion is justified.

30. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of patent involved in the present interference.

31. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, I will appear for cross examination within the United States during the time allotted for cross examination.

Dated: April 28, 2010



Risto Lammintausta, M.D., Ph.D.